REMARKS

Favorable reconsideration is respectfully requested in view of the foregoing amendments and following remarks.

Page 333 was objected to on the basis that the text was misaligned.

Page 333 has been replaced with a new copy of page 333 which is properly aligned.

Accordingly, the objection to the disclosure is deemed to be overcome.

Claims 26-31 were rejected under 35 USC 112, first paragraph, on the basis that the specification was not enabling for the breadth of the claims. This ground of rejection is respectfully traversed.

The effect of the claimed compounds in the treatment of the diseases other than diabetes and Alzheimer's disease as pointed out in the grounds of rejection under 35 USC 112, first paragraph, [i.e., neurodegenerative diseases (claims 27 and 28), diabetic complications (claim 29), disease due to malfunction of immune system (claim 30) and alopecia, breast cancer, non-small cell lung carcinoma, thyroid cancer, T or B-cell leukemia and virus-induced tumors (claim 31)] is clear from the experimental data of GSK-3β-inhibitory activity described in the present specification and the enclosed technical references. Please see the following 19 references cited in an IDS concurrently filed with this response to the Office Action.

1) Hoshi, M. *et al., Proc. Natl. Acad. Sci.* **93**, 2719-2723(1996)
2) D' Mello, S. R. *et al., Exp. Cell Res.* **211**, 332-338(1994)
3) Volonte, C. *et al., Neurosci. Letts.* **172**, 6-10(1994)
4) Nonaka, Chuang, *NeuroReport*, **9**, 2081-2084(1998)
5) Maggirwar, S. B. *et al., J. Neurochem.* **73**, 578-586(1999)
6) Stambolic, V. *et al., Curr. Biol.* **6**, 1664-1668(1996)
7) Klein, P. S. *et al., Proc. Natl. Acad. Sci.* **93**, 8455-8459(1996)
8) Chen, G. *et al. J. Neurochem.* **72**, 1327-1330(1999)
9) Nonaka, S. et *al. Proc. Natl. Acad. Sci.* **95**, 2642-2647(1998)
10) Beals, C. R. *et al., Science* **275**, 1930-1933(1997)
11) Graef, I. A. *et al., Nature* **401**, 703-708(1999)
12) Zhu, A. J. *et al., Development* **126**, 2285-2298(1999)
13) Davis, S. T. *et al., Science* **291**, 134-137(2001)
14) Lee, T. T. *et al., J. Cell. Biochem.* **58**, 474-480(1995)

15) Hoeflich, K. P. *et al.*, *Nature* **406**, 86-90(2000)
16) Milligan, S. A. *et al.*, *Anticancer Res.* **21**, 39-44(2001)
17) Romieu-Mourez, R. *et al.*, *Cancer Res.* **61**, 3810-3818(2001)
18) Nikoulina, S. E. *et al.*, *Diabetes*, **49**,263-271(2000)
19) Bhat, R. V. *et al.*, *Proc. Natl. Acad. Sci.* **97**, 11074-11079(2000)

The relevance of these references is described below.

Neurodegenerative diseases (claims 27-28)

A neurodegenerative disease means a disease wherein deposits derived from phosphorylated tau are found in the encephalic tissue as a neurofibrillary tangle, and generally refers to Alzheimer's disease, ischemic cerebrovascular disorders, Down's syndrome, cerebral ischemia due to cerebral amyloid angiopathy, progressive supranuclear paralysis, subacute sclerosing panencephalitic Parkinsonism, postencephalitic Parkinsonism, boxer's encephalopathy, Parkinsonism dementia complex of Guam, Lewy body disease, Pick's disease, corticobasal degeneration, frontotemporal dementia, AIDS encephalopathy, Huntington's disease, manic-depressive psychosis and the like.

GSK-3β is one of the enzymes involved in tau phosphorylation and, in the above-mentioned diseases, deposits derived from phosphorylated tau are found in the encephalic tissue as a neurofibrillary tangle. These deposits induce cell death of axon and neuritic dystrophy.

Moreover, pyruvate dehydrogenase (PDH) is phosphorylated and inactivated by GSK-3β[1]. As a result, the production amount of acetylcholine necessary for maintaining cell activity decreases and neuronal death is directly induced.

Accordingly, a GSK-3β inhibitor having a tau phosphorylation inhibitory activity and/or a PHD phosphorylation inhibitory activity can suppress neuronal death and cell death of axon, and is effective for the treatment of neurodegenerative diseases.

Diabetic complications (claim 29)

Inhibition of GSK-3 increases glycogen synthase activity and reduces the glucose level by conversion to glycogen. Therefore, it is effective for the treatment of diabetes.

Moreover, GSK-3 is known to be expressed in excess in the muscle of patients with type II diabetes[18]. Accordingly, a GSK-3 inhibitor is effective for the treatment of diabetes and diabetic complications such as diabetic neuropathy (e.g., algesthesia and decreased sensation and the like).

Immunopotentiator (claim 30)

Intracellular NF-AT (nuclear factor of activated T cell) is generally phosphorylated and inactivated. It has been shown in recent years that NF-AT is phosphorylated by GSK-3β and inactivated[10), 11)].

Accordingly, a GSK-3β inhibitor induces activation of NF-AT and differentiation and proliferation of T cell and has an immunopotentiating effect.

Alopecia, breast cancer, non-small cell lung carcinoma, thyroid cancer, T or B-cell leukemia and virus-induced tumors (claim 31)

Alopecia

The hair growth is controlled by a Wnt signaling pathway[12)], and therefore, a GSK-3 (α and β) inhibitor is effective for alopecia. In addition, a CDK inhibitor is effective for chemotherapy-induced alopecia[13)]. This is considered to be attributable to the inhibition of GSK-3 activity by a CDK inhibitor.

Accordingly, a GSK-3 inhibitor is effective for the treatment against alopecia.

Thyroid cancer

GSK-3 is known to be involved in the control of transcription factors. In thyroid carcinoma, thyroid adenoma and thyroid hyperplasia, kinaseF_A/GSK-3α activity significantly increases over the control[14)].

Accordingly, a GSK-3 inhibitor is effective for the treatment of thyroid cancer.

Breast cancer, non-small cell lung carcinoma, T or B-cell leukemia and virus-induced tumors

Abnormal activation of NF-$_K\beta$ plays a key role in the onset and progression of many carcinomas such as leukemia[15], non-small cell lung carcinoma[16], breast cancer[17] and the like.

On the other hand, a GSK-3β inhibitor is effective for breast cancer, non-small cell lung carcinoma and T or B-cell leukemia, because lithium, which is a GSK-3β inhibitor, weakens activation of NF-$_K\beta$ induced by TNFα[15].

In addition, adult T-cell leukemia/lymphoma (ATLL) is known to be triggered by infection with Human T-cell Lymphotropic Virus (HTLV-1). Thus, a GSK-3β inhibitor is effective for virus-induced tumors.

In view of the foregoing, it is respectfully submitted that the specification is enabling for claims 26-31 as amended, and that this ground of rejection has been overcome.

Claims 1-31 were rejected under 35 USC 112, second paragraph, as being indefinite for the reasons set forth in item 6 on pages 4-5 of the Action.

These grounds of rejection are deemed to be overcome in view of the foregoing amendments and following remarks.

1) The term used in the claims, "optical active form", has a clear meaning from the knowledge in the art and from the description in the present specification, page 37, lines 18-20, page 41, line 20 to page 42, line 3, Examples 116 and 117, and Examples 140 and 141.

2) In claims 1, 2 and 12, the phrase, "a group derived from" has been deleted.

3) Claims 26-31 have been rewritten in a method of use form in conformance with U.S. practice.

4) Claims 20-21 are deleted without prejudice.

5) In claims 26, 27, 29 and 31, the phrase "prevention and/or" has been deleted without prejudice.

6) As for the phrase "a disease caused by glycogen synthase kinase-3β hyperactivity" in claim 26, chronic or acute neurodegenerative diseases, cerebral infarction, AIDS encephalopathy, manic-depressive psychosis and the like are known. The present invention is effective for the treatment of these diseases, which is clear from the following description and the knowledge in the art.

Chronic or acute neurodegenerative diseases

The growth factor-mediated activation of P13K/Akt pathway plays an important role in the survival of neurons. Then this pathway is activated, GSK-3β is suppressed. In a recent report[19], high GSK-3β activity in neurodegeneration such as encephalic ischemia and the like, and in cellular and animal models after blocking of the growth factor, has been reported. In other words, it is considered that the GSK-3β activity is enhanced in neurons sensitive to apoptosis, and a kind of cell death occurs in chronic or acute degenerative diseases [e.g., Alzheimer's disease, Parkinsonism, amyotrophic lateral sclerosis, Huntington's disease, HIV dementia complex, ischemic attack, head injury and the like.] Accordingly, a GSK-3β inhibitor is effective for the treatment of these diseases.

Cerebral infarction

A GSK-3β inhibitor is considered to show a neuronal survival effect in the treatment of cerebral infarction [e.g., ischemic cerebrovascular disorders, cerebral ischemia due to cerebral amyloid angiopathy, etc.].

The grounds therefore are prevention of apoptosis in immature cerebellar granule neurons by lithium (Li^+) having a GSK-3β inhibitory activity[2), 3)], and neuroprotective effects of chronic lithium on focal cerebral ischemia in rats (middle cerebral artery occulution model)[4)].

Accordingly, a GSK-3β inhibitor is effective for the treatment of cerebral infarction.

AIDS encephalopathy

Tat, which is an HIV virus producing protein, improves GSK-3β activity of nerve cells and causes nerve cell death[5].

Accordingly, a GSK-3β inhibitor is effective for the treatment of AIDS encephalopathy.

Manic-depressive psychosis

Manic-depressive psychosis is characterized by manic episode and depressive episode. Lithium and valproate have been used for the treatment based on a mood stabilizing effect. The defect of lithium is a narrow therapeutic window and a risk of lithium intoxication due to excessive administration. On the other hand, lithium and valproate have been reported to inhibit GSK-3 at a concentration used for treatment[6), 7), 8)]. While the correlation between anti-depressive activity and GSK-3β inhibitory activity is not clear, an inhibitory activity for glutamate-induced toxicity[9)] is considered to partly responsible for the maintained activity of nerve cell.

From the above, it is clear that a GSK-3β inhibitor is effective for the improvement of manic-depressive psychosis and is free of a risk associated with lithium and the like.

In view of the foregoing, it is respectfully submitted that the scope and meaning of the claims is definite under 35 USC 112, second paragraph, and that this ground of rejection is deemed to be overcome.

Claims 26-31 were rejected under 35 USC 101 as failing to set forth process steps.

This ground of rejection is deemed to be overcome in view of the foregoing amendments.

Lastly, claims 1, 2, 4, 5 and 20-31 were rejected under 35 USC 102 as anticipated by De Wald. This ground of rejection is respectfully traversed as applied to the amended claims.

USP 3,790,576 discloses 4,9-dihydro-1H-pyrazolo[3,4-b]quinoline compounds having the formula I. In the compound disclosed in USP 3,790,576, two R^4 are attached to the 4-position and R^4 is methyl or ethyl (see USP 3,790,576, column 1 and Examples 1-10).

In the claims of the present invention, "alkyl" has been deleted from the definition R^3.

Thus, the claims as amended are directed to different compounds than those disclosed in USP 3,790,576. In addition, the present invention is not disclosed or suggested in USP 3,790,576. From the foregoing, the rejection under 35 USC 102(b) is overcome.

In view of the foregoing, it is believed that each ground of rejection set forth in the Official Action has been overcome, and that the application is now in condition for allowance. Accordingly, such allowance is solicited.

Respectfully submitted,

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dihydro-6-propyl-2*H*-pyrazolo[3,4-*b*]pyridine, a tautomer thereof, an optically active form thereof, or a pharmaceutically acceptable salt thereof.

20. A medicament comprising a dihydropyrazolopyridine compound of claim 1 or 2, an optically active form thereof, a pharmaceutically acceptable salt thereof or a hydrate thereof.

21. A medicament comprising a dihydropyrazolopyridine compound of claim 12 or 13, an optically active form thereof, or a pharmaceutically acceptable salt thereof.

22. A pharmaceutical composition comprising a dihydropyrazolopyridine compound of claim 1 or 2, an optically active form thereof, a pharmaceutically acceptable salt thereof or a hydrate thereof, and a pharmaceutically acceptable additive.

23. A pharmaceutical composition comprising a dihydropyrazolopyridine compound of claim 12 or 13, an optically active form thereof, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable additive.

24. A glycogen synthase kinase-3 beta inhibitor comprising a compound selected from the group consisting of a dihydropyrazolopyridine compound of claim 1 or 2, an optically active form thereof, a pharmaceutically acceptable salt thereof and a hydrate thereof.

25. A glycogen synthase kinase-3 beta inhibitor comprising a compound selected from the group consisting of a dihydropyrazolopyridine compound of claim 12 or 13, an